NIHR | Biomedical Research Centre at The Royal Marsden and the ICR

PHD STUDENTSHIP PROJECT PROPOSAL: BRC PROJECTS	
PROJECT DETAILS	
Project Title	Can artificial intelligence predict outcome in patients receiving stereotactic radiosurgery of brain metastasis?
Short Project Title	**BLACKLEDGE: AI for improved prediction in brain mets**
SUPERVISORY TEAM	
Primary Supervisor	Matthew Blackledge
Associate Supervisor(s)	Nicola Rosenfelder, Liam Welsh, Emma Harris
Secondary Supervisor	Uwe Oelfke
DIVISIONAL AFFILIATION	
Primary Division	Radiotherapy and Imaging
Primary Team	Computational Imaging
Site	Sutton
Other Division	Radiotherapy and Imaging
Other Team	Imaging for Radiotherapy Adaptation
PROJECT PROPOSAL	

BACKGROUND TO THE PROJECT

The incidence and prevalence of brain metastases (BM) has increased over the last few years as advances in cancer treatments have led to better extracranial disease control and survival. Survival *with* BM has also improved significantly from a few months to 1 or more years with better understanding and treatment of BM. All patients with BM are considered at increased risk of seizures and are warned of this when diagnosed, and all are immediately banned from driving. Patients report significant detrimental consequences from this including increased social isolation, anxiety, loss of confidence and inability to work. However, we know that the majority will never have a seizure, and many will live the remainder of their lives in unnecessary fear. Furthermore, screening for BM is now undertaken more frequently in asymptomatic patients and smaller sites of disease detectable with newer MRI methods.

Stereotactic radiosurgery (SRS) is a highly-targeted form of radiotherapy used to treat BM. Treatment response is assessed with 3-monthly MRI scans but interpretation is challenging as SRS-related brain injury, 'radionecrosis', in responding patients can mimic disease progression and confound radiological assessment. Treatment of progressive disease is drastically different from treatment of radionecrosis and better response assessment is urgently needed to allow accurate MRI interpretation without needing to await serial scan results. The SAFER study (CCR:5266, CI:Nicola Rosenfelder), aims to determine which clinical- and MRI-features increase seizure-risk post-SRS using 3-monthly MRIs.

In this proposed project, the student will develop novel approaches using artificial intelligence and deep-learning to improve seizure-risk-stratification and response evaluation post-SRS for BM by combining clinically-relevant data sources including MR-imaging, patient demographics, and radiotherapy dose. These new algorithms will be tested and verified within the context of the SAFER study. Technical outcomes of this project will be highly applicable to cancer research utilising imaging data and radiotherapy.

PROJECT AIMS

- Develop new multi-parametric deep-learning (DL) algorithms that combine MR-imaging data with patient demographics and radiation dose to predict risk and response in cancer.

- Provide 'explainability' to the proposed algorithms and identify the importance of each of the data sources in predicting patient outcome.

- Test the accuracy of proposed algorithms in predicting the patient-specific risk of
    1. Seizure events due to presence of brain metastases.
    2. Tumour response from patient survival.
    3. Radionecrosis versus progressive disease

- Compare and contrast such deep-learning approaches with traditional statistical approaches including radiomics.

- Collate developed tools into robust research software that can be used for analysis of clinical trial data by radiologists.

RESEARCH PROPOSAL

The number of patients living with brain metastases (BM) has increased significantly over the last 5-10 years. In 2010, it was estimated that BM occurs in 20-40% of patients with systemic cancer[1], but this is likely to be considerably higher now. The increase is due to a combination of improved survival resulting from better systemic treatment options (in particular immunotherapy and targeted therapies) leading to enhanced extracranial disease control, and better treatment of intracranial disease using targeted intracranial treatments such as surgery or high-precision, high-dose radiation, termed 'stereotactic radiosurgery' (SRS)[2]. Median survival for BM patients undergoing SRS is now ~11-15 months[3], and for some patients, is measured in years.

The primary ***hypothesis*** of this project is that deep-learning approaches that combine data from various sources (imaging, clinical and radiodosimetric) can improve the prediction accuracy of local control and BM-related seizure events, over radiational statistical approaches that include only basic imaging assessment such as tumour size. An additional hypothesis is that deep-learning can accurately distinguish radionecrosis from tumour progression using MR-imaging data, and thus drastically improve treatment decision making in patients with brain metastasis.

The PhD will leverage data generated by the SAFER study, led by Dr Nicola Rosenfelder: The study aims to prospectively collect imaging data and clinical information from 375 patients receiving SRS for treatment of brain metastasis at the Royal Marsden until the end of 2022. Patients will have a 24-month follow-up period after SRS in order to establish patient outcome, with between 60 and 75 patients expected to experience seizures during this period. MRI will be performed before and after SRS treatment, and then at 3-monthly intervals during the patient follow-up period; imaging will include standard morphological and diffusion-weighted MRI (DWI)[4], and also explore delayed contrast extravasion MRI[5] for identification of tissues with persistently enhancing characteristics. This study is currently under HRA review with recruitment planned to start in 2021, and is not contingent on funding.

In addition to addressing the clinical unmet need for tools to predict survival and the incidence of seizure in BM patients, an important key contribution of this PhD to the field of deep learning will be novel methods to combine patient clinical data, radiotherapy dose, and longitudinal imaging data. Incorporation of the latter is a complex problem and has yet to be fully explored, and methods developed for the inclusion of imaging time-series will be highly innovative. The proposed pipelines will also be applicable to future clinical studies of clinical and radiological response to cancer treatment and is particularly relevant to studies of the magnetic resonance linac (MRL) which generates serial MRI images during the course of treatment in addition to those obtained during follow-up.

Research Timeline

Year 1 (2021-22):

- The student will complete training modules provided by the ICR through the online "Perspectives in Oncology" course. This will provide the student with a core understanding of cancer biology, cancer therapeutics and bioinformatics, which are key components of the Institute's scientific strategy. This will be complemented with specialised training offered by the ICR and Royal Marsden in medical physics and MR-imaging.
- The first research task will be to test different approaches to spatial registration of brain MR-imaging data (i) between different patients, and (ii) between different scans for the same patient. Whole brain delineation will be used to assess the accuracy of these approaches in terms of maximum dice-coefficient (brain overlap), using existing data from the SAFER study.
- Using these results, the student will then investigate different approaches to automatic brain-region classification using available state-of-the-art brain atlases/templates[6]. This will provide the spatial context required in future development of deep-learning architectures and familiarise the student with image processing pipelines.
- The results obtained from this initial research objective will be developed into a submission to a relevant conference; this conference would provide the student with knowledge of the state-of-the-art techniques in AI/imaging research.

Year 2 (2022-23):

- The student will develop a practical knowledge of artificial intelligence paradigms, concentrating on the implementation of deep-learning solutions in packages such as TensorFlow and Keras, alongside traditional machine-learning approaches. They will also familiarise themselves with the concepts of imaging biomarker research and novel deep-learning-based survival analysis techniques such as DeepSurv[7].
- Using these approaches, they will construct an automatic delineation/segmentation pipeline (e.g. with the "U-Net" deep-learning architecture[8]) for regions of brain disease, using radiotherapy planning contours on baseline scans as a gold-standard (N = 375). Data will be split into the train:validate:test ratios of 3:1:1.
- The accuracy of post-treatment segmentation will be further evaluated on patient-follow up scans to provide an automated approach to tracking tumour volume changes following treatment.
- Using the segmentation methodology, the student will extract radiomic features from tumour regions using an existing technology (pyRadiomics).
- Results from the tumour segmentation study will be collated into a paper for submission in a relevant medical physics journal.

Year 3 (2023-2024):

- The student will construct a deep learning pipeline to (i) predict patient survival and (ii) predict the occurrence of seizures and (iii) distinguish tumour progression from radionecrosis,. This pipeline will naturally incorporate patient demographic, MR-imaging and radiotherapy dose profile data; an illustration of such a network for seizure prediction is provided in the **Figure** below.
- It is the intention that a single deep-learning architecture will be sufficient for all three outcomes investigated, using minor changes to the final layer of the network. Should this not be possible, the student will need to investigate whether alternative architectures would be more suitable.
- Innovative objectives of this network will be to (i) ensure that it can incorporate imaging data from serial time-points (baseline and follow-up imaging), and (ii) utilise the multi-parametric MRI available in the SAFER study.

- The follow-up duration for the majority of patients from the SAFER study will be complete towards the end of this academic year. Data will again be split according to ratios 3:1:1; accuracy of the different models will be compared using the validation data alone.
- Models that include or exclude different input data will be compared to identify whether inclusion of all inputs is required for accurate outcome prediction or only a subset. Such a comparison is crucial for understanding how these algorithms work, which is a key component of the NHS code of conduct for data-driven health and care technology (see **Figure**).
- The accuracy of deep-learning models for the three desired outputs will be compared against traditional statistical approaches that use the radiomic features extracted from tumours in year 2.
- It is expected that the student will author a paper to discuss the technical detail of their deep-learning architecture.

Year 4 (2024-2025):

- Using the test cohort of the SAFER study, the final accuracy of the proposed algorithm will be evaluated for all three predicted outcomes; results will be collated into a draft paper for submission to a relevant journal.
- The established pipeline will be compiled into a plugin for a medical image-viewing platform (OsiriX) so that it may be further tested as a prototype research tool in ongoing brain studies.
- The student will spend the final 6-8 months of their project writing their thesis and writing a paper that discusses the clinical findings of their work.

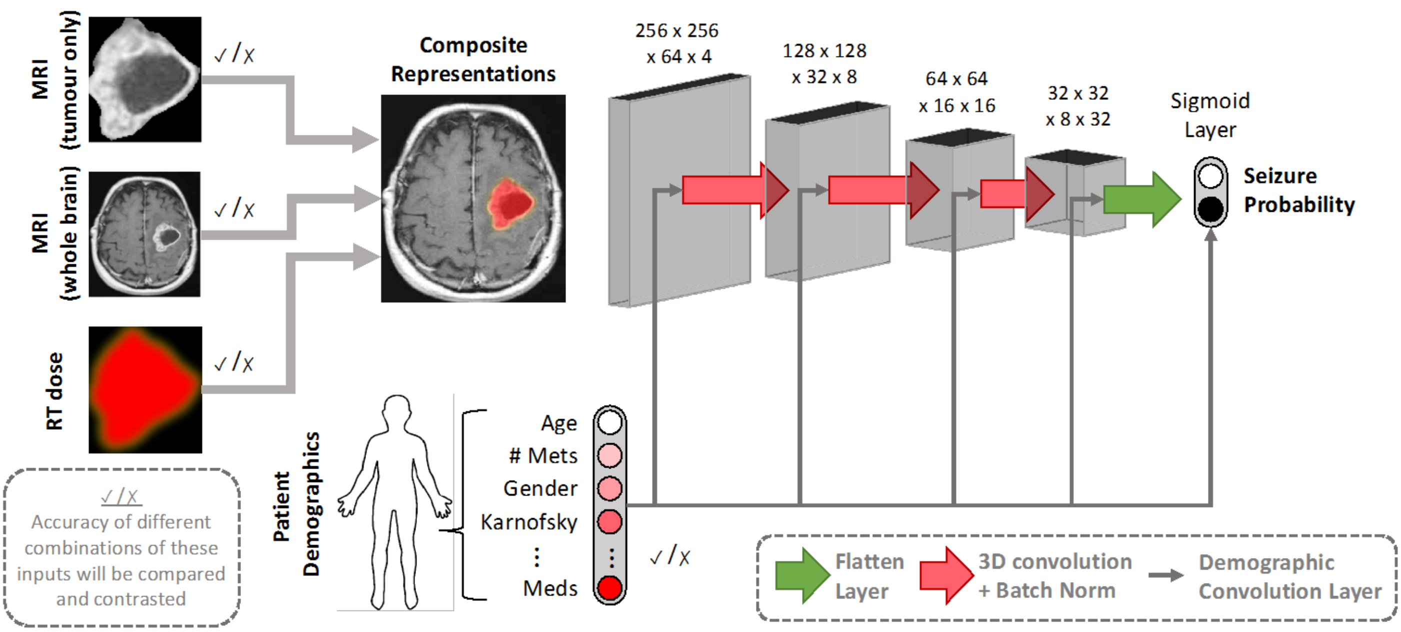

Figure: An illustration of a potential deep-learning pipeline for this studentship. Using a novel demographic convolutional layer developed at the ICR, the student will be able to combine different data-sources to improve prediction accuracy of seizure events over traditional methods. By including/excluding different inputs to this network, the student will be able to investigate which data sources are most valuable when making these predictions. For example, inclusion/exclusion of the whole brain as an input would determine whether appearances of background regions of healthy brain, or location of the tumour within the brain are important factors in making predictions on seizure risk rather than just tumour characteristics alone. This network is for illustrative purposes only and the student is expected to develop their own innovative solutions to this task, building on the work currently done within the computational imaging lab.

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LITERATURE REFERENCES

1. Linskey, M. E. *et al.* The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline. *Journal of Neuro-Oncology* (2010) doi:10.1007/s11060-009-0073-4.
2. Soliman, H., Das, S., Larson, D. A. & Sahgal, A. Stereotactic radiosurgery (SRS) in the modern management of patients with brain metastases. *Oncotarget* (2016) doi:10.18632/oncotarget.7131.
3. Gorovets, D. *et al.* Predictors for long-term survival free from whole brain radiation therapy in patients treated with radiosurgery for limited brain metastases. *Front. Oncol.* (2015) doi:10.3389/fonc.2015.00110.
4. Koh, D. M. *et al.* Whole-body diffusion-weighted mri: Tips, tricks, and pitfalls. *American Journal of Roentgenology* vol. 199 252–262 (2012).
5. Zach, L. *et al.* Delayed contrast extravasation MRI: A new paradigm in neuro-oncology. *Neuro. Oncol.* (2015) doi:10.1093/neuonc/nou230.
6. Fischl, B. FreeSurfer. *NeuroImage* (2012) doi:10.1016/j.neuroimage.2012.01.021.
7. Katzman, J. L. *et al.* DeepSurv: Personalized treatment recommender system using a Cox proportional hazards deep neural network. *BMC Med. Res. Methodol.* (2018) doi:10.1186/s12874-018-0482-1.
8. Ronneberger, O., Fischer, P. & Brox, T. U-Net: Convolutional Networks for Biomedical Image Segmentation. *Miccai* 234–241 (2015) doi:10.1007/978-3-319-24574-4_28.

CANDIDATE PROFILE	
Note: the ICR’s standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1)	
Pre-requisite qualifications of applicants	BSc or equivalent in Physics, Maths or Computer Science
Intended learning outcomes	• In-depth knowledge of MRI physics, specialising in the acquisition of diffusion-weighted imaging and contrast-enhanced imaging. • Deep-learning and applications to survival analysis. • Medical imaging processing and data curation • Multi-parametric approaches to biomarker discovery in cancer research

ADVERTISING DETAILS	
Project suitable for a student with a background in Please tick all categories that apply – your project will be advertised under all selected categories	☐ Biological Sciences X Physics or Engineering ☐ Chemistry ☐ Mathematics, Statistics or Epidemiology

	X Computer Science ☐ Other (provide details)
Keywords	**1. Medical Physics**
	2. Artificial Intelligence
	3. Brain Metastasis
	4. Machine Learning
	5. Magnetic Resonance Imaging
	6. Computer Vision